

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: O. Axelsson, et al. Group Art Unit: To be assigned
Serial Number: To be assigned Examiner: To be assigned
Filing Date: November 16, 2001
Title: Process for Preparation of MR Contrast Agents

FIRST PRELIMINARY AMENDMENT

Honorable Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a continuation of international application number PCT/GB00/01897 filed May 17, 2000. This application also claims priority to application number 9911681.6 filed May 19, 1999 in Great Britain. Additionally, this application claims the benefit of United States provisional application number 60/139,259 filed June 15, 1999.

In the Specification

Please amend the title at page 1, line 1, as follows:

Process for Preparation of MR Contrast Agents

Please amend page 1, line 3, by inserting the following sentence and heading:

--This application is a continuation application of international application number PCT/GB00/01897 filed May 17, 2000, the entire disclosure of which is hereby incorporated by reference.

Background of Invention--

Please amend page 2, line 33, by inserting the following paragraph and heading:

--While WO99/24080 does describe means by which para-hydrogen hydrogenation may be effected, we have now found that hydrogenation to harness for MRI the p-H₂ and/ or o-D₂ induced hyperpolarization, the hydrogenation reaction is particularly favourably performed by mixing gaseous para-hydrogen and/or ortho-deuterium enriched hydrogen (i.e. where the p:o ratio of ¹H₂ is greater than 1:3, particularly greater than 3:7, more particularly greater than 1:1 and/or the o:p ratio of ²H₂ is greater than 3:2, particularly greater than 3:1, more particularly greater than 4:1) with a spray of a solution of the unsaturated compound and a hydrogenation catalyst.

Summary of Invention--

Please amend page 3, lines 17-27, by deleting the following paragraph:

[While WO99/24080 does describe means by which para-hydrogen hydrogenation may be effected, we have now found that hydrogenation to harness for MRI the p-H₂ and/ or o-D₂ induced hyperpolarization, the hydrogenation reaction is particularly favourably

performed by mixing gaseous para-hydrogen and/or ortho-deuterium enriched hydrogen (i.e. where the p:o ratio of $^1\text{H}_2$ is greater than 1:3, particularly greater than 3:7, more particularly greater than 1:1 and/or the o:p ratio of $^2\text{H}_2$ is greater than 3:2, particularly greater than 3:1, more particularly greater than 4:1) with a spray of a solution of the unsaturated compound and a hydrogenation catalyst.]

Please amend page 5, line 35, by inserting the following paragraph and headings:

--Brief Description of the Figures

Figure 1 is a schematic view of one apparatus according to the invention;

Figure 2 is a schematic view of part of the apparatus of Figure 1;

Figure 3 is a schematic view of a further part of the apparatus of Figure 1; and

Figure 4 is a schematic view of a further aspect of the present invention.

Detailed Description of the Invention--

Please amend page 13, lines 8-19, by deleting the following text:

[Embodiments of the process and apparatus of the invention will now be described with reference to the following non-limiting Example and to the accompanying drawings, in which:

Figure 1 is a schematic view of one apparatus according to the invention;

Figure 2 is a schematic view of part of the apparatus of Figure 1;

Figure 3 is a schematic view of a further part of the apparatus of Figure 1; and

Figure 4 is a schematic view of a further aspect of the present invention.]

Please amend page 15, line 5, by inserting the following heading and paragraph:

--Examples

The following example is illustrative of certain preferred embodiments of the invention but is not intended to be illustrative of all embodiments.--

Please amend page 17, line 23, by inserting the following paragraph:

-- It is apparent that many modifications and variations of the invention as hereinabove set forth may be made without departing from the spirit and scope thereof. The specific embodiments described are given by way of example only, and the invention is limited only by the terms of the appended claims.--

In the Claims

Please amend page 18, line 1, as follows:

[Claims]

What is claimed is:

Please cancel claim 13, without prejudice.

Please amend claim 1 as follows:

1. (once amended) A process for the preparation of an MR contrast agent[, said process] comprising:
 - i) obtaining a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of said substrate compound;
and
 - ii) introducing said solution in droplet form into a chamber containing hydrogen gas (H_2) enriched in para-hydrogen ($p\text{-}^1H_2$) and/or ortho-deuterium ($o\text{-}^2H_2$) [whereby]to hydrogenate said substrate to form a hydrogenated imaging agent[;
 - iii) optionally subjecting said hydrogenated imaging agent to a magnetic field having a field strength below earth's ambient field strength;
 - iv) optionally dissolving said imaging agent in an aqueous medium;
 - v) optionally separating said catalyst from the solution of said imaging agent in said aqueous medium;
 - vi) optionally separating said solvent from the solution of said imaging agent in said aqueous medium; and
 - vii) optionally freezing the solution of said imaging agent in said aqueous medium].

Please amend claim 2 as follows:

2. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is less than 50 μ T.

Please amend claim 3 as follows:

3. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is less than 1 μ T.

Please amend claim 4 as follows:

4. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is less than or equal to 0.1 μ T.

Please amend claim 5 as follows:

5. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is cycled in a first part from earth's ambient field strength to a field strength less than 0.1 μ T, [then]and in a second part back to ambient field strength again.

Please amend claim 6 as follows:

6. (once amended) [A]The process [as claimed in]of claim 5 wherein the first part of the cycle is [of the order of]approximately ≤ 1 ms and the second part is [of the order of]approximately 10-10000 ms.

Please amend claim 7 as follows:

7. (once amended) [A]The process [as claimed in any one of the preceding claims]of claim 1 wherein said process is carried out directly in water and wherein both said substrate and said catalyst are water-soluble.

Please amend claim 9 as follows:

9. (once amended) [An]The apparatus [as claimed in]of claim 8 wherein said hydrogenation apparatus is further provided with magnetic shielding such that the magnetic field within at least part of said hydrogenation chamber and/or within at least part of said conduit is $<50 \mu\text{T}$.

Please amend claim 10 as follows:

10. (once amended) [An]The apparatus [as claimed in]of claim 9 wherein said magnetic field is $<1 \mu\text{T}$.

Please amend claim 11 as follows:

11. (once amended) [An]The apparatus [as claimed in]of claim 9 wherein said magnetic field is $<0.1 \mu\text{T}$.

Please amend claim 12 as follows:

12. (once amended) [An]The apparatus [as claimed in any one of claims 8 to 11]of claim 8 wherein said conduit is provided with a liquid inlet between said hydrogenation chamber and said catalyst removal chamber.

Please add new claim 14 as follows:

14. (new) The process of claim 1 further comprising subjecting said hydrogenated imaging agent to a magnetic field having a field strength at or below the ambient magnetic field strength of the earth.

Please add new claim 15 as follows:

15. (new) The process of claim 1 further comprising dissolving said imaging agent in an aqueous medium.

Please add new claim 16 as follows:

16. (new) The process of claim 14 further comprising separating said catalyst from said solution of imaging agent in aqueous medium.

Please add new claim 17 as follows:

17. (new) The process of claim 14 further comprising separating said solvent from said solution of imaging agent in aqueous medium.

Please add new claim 18 as follows:

18. (new) The process of claim 14 further comprising freezing solution of imaging agent in aqueous medium.

Remarks

Applicants have amended the specification to cross reference the parent application which is a PCT application designating the United States. Applicants have also amended the specification to add the required headings and move the text to be in the required order. A copy of the specification encompassing the amendments is attached hereto.

Applicants have amended claims 1-7 and 9-12. Applicants have cancelled claim 13, without prejudice and have added new claims 14-18. A version of the claims marked up to show the amendments, as well as a clean version of the claims encompassing the amendments, is attached hereto.

Applicants are submitting herewith a copy of the International Search Report which issued on International Application number PCT/GB00/01897, of which the present application is a continuation. All of the publications cited in the International Search Report are listed on the attached Information Disclosure Statement.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Respectfully submitted,



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Specification (marked-up version showing amendments)

Page 1, line 1:

Process for Preparation of MR Contrast Agents

Page 1, line 3, insertion of:

This application is a continuation application of international application number PCT/GB00/01897 filed May 17, 2000, the entire disclosure of which is hereby incorporated by reference.

Background of Invention

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While WO99/24080 does describe means by which para-hydrogen hydrogenation may be effected, we have now found that hydrogenation to harness for MRI the p-H₂ and/or o-D₂ induced hyperpolarization, the hydrogenation reaction is particularly favourably performed by mixing gaseous para-hydrogen and/or ortho-deuterium enriched hydrogen (i.e. where the p:o ratio of ¹H₂ is greater than 1:3, particularly greater than 3:7, more particularly greater than 1:1 and/or the o:p ratio of ²H₂ is greater than 3:2, particularly greater than 3:1, more particularly greater than 4:1) with a spray of a solution of the unsaturated compound and a hydrogenation catalyst.

Summary of Invention

Page 3, lines 17-27, deletion of:

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Page 5, line 35, insertion of:

Brief Description of the Figures

Figure 1 is a schematic view of one apparatus according to the invention;

Figure 2 is a schematic view of part of the apparatus of Figure 1;

Figure 3 is a schematic view of a further part of the apparatus of Figure 1; and

Figure 4 is a schematic view of a further aspect of the present invention.

Detailed Description of the Invention

Page 13, lines 8-19, deletion of:

[Embodiments of the process and apparatus of the invention will now be described with reference to the following non-limiting Example and to the accompanying drawings, in which:

Figure 1 is a schematic view of one apparatus according to the invention;

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Figure 4 is a schematic view of a further aspect of the present invention.]

Page 15, line 5, insertion of:

Examples

The following example is illustrative of certain preferred embodiments of the invention but is not intended to be illustrative of all embodiments.

Page 17, line 23, insertion of:

It is apparent that many modifications and variations of the invention as hereinabove set forth may be made without departing from the spirit and scope thereof. The specific embodiments described are given by way of example only, and the invention is limited only by the terms of the appended claims.

Claims (marked-up version showing amendment(s))

Page 18, line 1:

[Claims]

What is claimed is:

1. (once amended) A process for the preparation of an MR contrast agent[, said process] comprising:
 - i) obtaining a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of said substrate compound;
and
 - ii) introducing said solution in droplet form into a chamber containing hydrogen gas (H_2) enriched in para-hydrogen ($p\text{-}^1H_2$) and/or ortho-deuterium ($o\text{-}^2H_2$)
[whereby]to hydrogenate said substrate to form a hydrogenated imaging agent[;
 - iii) optionally subjecting said hydrogenated imaging agent to a magnetic field having a field strength below earth's ambient field strength;
 - iv) optionally dissolving said imaging agent in an aqueous medium;
 - v) optionally separating said catalyst from the solution of said imaging agent in said aqueous medium;
 - vi) optionally separating said solvent from the solution of said imaging agent in said aqueous medium; and

vii) optionally freezing the solution of said imaging agent in said aqueous medium].

2. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is less than 50 μT .
3. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is less than 1 μT .
4. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is less than or equal to 0.1 μT .
5. (once amended) [A]The process [as claimed in claim 1]of claim 14 wherein said field strength in step (iii) is cycled in a first part from earth's ambient field strength to a field strength less than 0.1 μT , [then]and in a second part back to ambient field strength again.
6. (once amended) [A]The process [as claimed in]of claim 5 wherein the first part of the cycle is [of the order of]approximately ≤ 1 ms and the second part is [of the order of]approximately 10-10000 ms.

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7. (once amended) [A]The process [as claimed in any one of the preceding claims]of claim 1 wherein said process is carried out directly in water and wherein both said substrate and said catalyst are water-soluble.
 9. (once amended) [An]The apparatus [as claimed in]of claim 8 wherein said hydrogenation apparatus is further provided with magnetic shielding such that the magnetic field within at least part of said hydrogenation chamber and/or within at least part of said conduit is $<50 \mu\text{T}$.
 10. (once amended) [An]The apparatus [as claimed in]of claim 9 wherein said magnetic field is $<1 \mu\text{T}$.
 11. (once amended) [An]The apparatus [as claimed in]of claim 9 wherein said magnetic field is $<0.1 \mu\text{T}$.
 12. (once amended) [An]The apparatus [as claimed in any one of claims 8 to 11]of claim 8 wherein said conduit is provided with a liquid inlet between said hydrogenation chamber and said catalyst removal chamber.
 14. (new) The process of claim 1 further comprising subjecting said hydrogenated imaging agent to a magnetic field having a field strength at or below the ambient magnetic field strength of the earth.

Claims (clean version encompassing amendments)

What is claimed is:

1. (once amended) A process for the preparation of an MR contrast agent comprising:
 - i) obtaining a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of said substrate compound; and
 - ii) introducing said solution in droplet form into a chamber containing hydrogen gas (H_2) enriched in para-hydrogen ($p\text{-}^1H_2$) and/or ortho-deuterium ($o\text{-}^2H_2$) to hydrogenate said substrate to form a hydrogenated imaging agent.
2. (once amended) The process of claim 14 wherein said field strength in step (iii) is less than $50\ \mu T$.
3. (once amended) The process of claim 14 wherein said field strength in step (iii) is less than $1\ \mu T$.
4. (once amended) The process of claim 14 wherein said field strength in step (iii) is less than or equal to $0.1\ \mu T$.

5. (once amended) The process of claim 14 wherein said field strength in step (iii) is cycled in a first part from earth's ambient field strength to a field strength less than $0.1 \mu\text{T}$, and in a second part back to ambient field strength again.
6. (once amended) The process of claim 5 wherein the first part of the cycle is approximately $\leq 1 \text{ ms}$ and the second part is approximately 10-10000 ms.
7. (once amended) The process of claim 1 wherein said process is carried out directly in water and wherein both said substrate and said catalyst are water-soluble.
8. A hydrogenation apparatus comprising a hydrogenation chamber having a liquid outlet into a conduit leading to a liquid droplet generator inlet to a solvent removal chamber,
said hydrogenation chamber having a hydrogen inlet and a solution inlet provided with a further liquid droplet generator,
said conduit including a catalyst removal chamber between said hydrogenation chamber and said solvent removal chamber and being provided with a liquid inlet, said solvent removal chamber being provided with a gas outlet and with a liquid outlet.
9. (once amended) The apparatus of claim 8 wherein said hydrogenation apparatus is further provided with magnetic shielding such that the magnetic field within at

least part of said hydrogenation chamber and/or within at least part of said conduit is $<50 \mu\text{T}$.

10. (once amended) The apparatus of claim 9 wherein said magnetic field is $<1 \mu\text{T}$.
11. (once amended) The apparatus of claim 9 wherein said magnetic field is $<0.1 \mu\text{T}$.
12. (once amended) The apparatus of claim 8 wherein said conduit is provided with a liquid inlet between said hydrogenation chamber and said catalyst removal chamber.
14. (new) The process of claim 1 further comprising subjecting said hydrogenated imaging agent to a magnetic field having a field strength at or below the ambient magnetic field strength of the earth.
15. (new) The process of claim 1 further comprising dissolving said imaging agent in an aqueous medium.
16. (new) The process of claim 14 further comprising separating said catalyst from said solution of imaging agent in aqueous medium.
17. (new) The process of claim 14 further comprising separating said solvent from said solution of imaging agent in aqueous medium.

18. (new) The process of claim 14 further comprising freezing solution of imaging agent in aqueous medium.

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